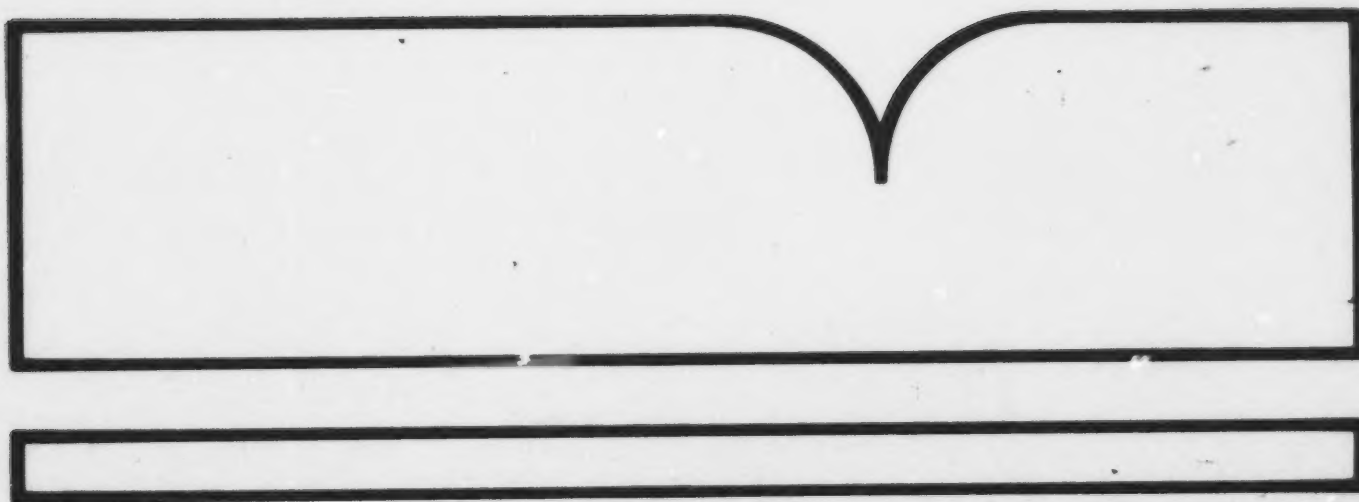


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Health and Environmental Effects
Profile for Ethyl Acetate

(U.S.) Environmental Protection Agency
Cincinnati, OH

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16. ABSTRACT The Health and Environmental Effects Profile for <u>Ethyl Acetate</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Ethyl acetate</u> has been determined to be a systemic toxicant. A Reference Dose (RFD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for <u>ethyl acetate</u> is <u>0.9 mg/kg/day</u> for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>ethyl acetate</u> is <u>1000</u> .					
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR ETHYL ACETATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Ethyl acetate is a clear, colorless, volatile liquid with a characteristic fruity odor (Windholz, 1983; Verschueren, 1983). It is soluble in various organic solvents and in water. In 1984, four U.S. manufacturers reported production of 210.425 million pounds of ethyl acetate (USITC, 1985). Excluding exports, ~97% of the ethyl acetate produced is used as a solvent and ~3% is used in chemical syntheses (CMR, 1986). About 64% of solvent use involves coating applications (CMR, 1986).

When released to water, microbial degradation and volatilization are likely to be important removal mechanisms. Ethyl acetate has been shown to be readily biodegradable in a number of BOD studies (using activated sludge and sewage), in a natural water BOD test and under anaerobic conditions (Stover and Kincannon, 1983; Price et al., 1974; Thom and Agg, 1975). The volatilization half-life from a river 1 m deep flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec has been estimated to be ~9 hours from the experimentally measured vapor-aqueous solution equilibrium ratio (Hine and Mookerjee, 1975). Hydrolysis will not be important in neutral or acidic water, but may become significant in alkaline water; the respective hydrolysis half-lives at 25°C and pHs 7, 8 and 9 are 2.0 years, 73 days and 7.3 days (Mabey and Mill, 1978). Aquatic oxidation (by HO radical), adsorption to sediment, and bioconcentration are not expected to be important (Anbar and Neta, 1967). If released to the atmosphere, ethyl acetate will react with photochemically produced HO radical with an estimated half-life of 5.5-5.9 days at 19-23°C (Atkinson, 1985). If released to soil, ethyl acetate is likely to be susceptible to significant leaching and biodegradation. Volatilization from dry surfaces is expected to be relatively rapid.

Ethyl acetate has been qualitatively detected in drinking water (Keith et al., 1976; Akiyama et al., 1980; Fielding et al., 1981), surface water (Ewing et al., 1977; Dewalle and Chian, 1978; Yasuhara et al., 1981), wastewater effluents (Ellis et al., 1982; U.S. EPA, 1984) and leachate/groundwater from landfills (Sabel and Clark, 1984). It is a small volume component of beer (Reed, 1984) and vinegar (Webb, 1983; Rogers and Fischetti, 1980) and has been found in human breast milk (Pellizzari et al., 1982). It has been identified in urban ambient air (Pellizzari et al., 1976; Ioffe et al., 1977; Holzer et al., 1977) and in the ambient rural air of a U.S. national forest (Holzer et al., 1977). Evaporation of ethyl acetate used as a solvent is probably the greatest man-made source of exposure to the compound in the atmosphere. Ethyl acetate is also a naturally occurring compound; it was detected in volatile emissions from plants and trees (Nicholas, 1973; Isidorov et al., 1985), microbes and animal waste (Graedel, 1978). It is emitted from contaminated beef as a result of microbial growth (Dainty et al., 1985), from stored household wastes (Kamiya and Ose, 1981) and from fermented eggs (Bullard et al., 1978). Emissions from whiskey fermentation contain ethyl acetate (Carter and Linsky, 1974), and it has also been identified in tobacco smoke (Schumacher et al., 1977; Holzer et al., 1976), and in exhaled air from normal humans (Conkle et al., 1975; Krotoszynski et al., 1979).

LC₅₀ values of 125-270 mg/l were reported for various fish and amphibian species (see Table 6-1), with medaka, Oryzias latipes, having the lowest LC₅₀ (Slooff et al., 1983). LC₅₀ values of 130-3950 mg/l were reported for various invertebrates, with the stonefly, Nemoura cinerea, having the lowest value (Slooff, 1983). The lowest reported acutely toxic concentration for fish or invertebrates was 19.4 mg/l, which inhibited growth of fathead minnows in a 96-hour exposure (Barron and Adelman, 1984).

The only chronic toxicity data were provided by a 32-day fathead minnow embryo-larval bioassay in which growth was impaired at concentrations of ≥ 9.65 mg/l (Barron and Adelman, 1984). Among aquatic plants and bacteria, Scenedesmus sp. were by far the most sensitive, having a threshold for inhibition of cell multiplication of 15 mg/l (Bringmann and Kuehn, 1978; Slooff et al., 1983).

Ethyl acetate was absorbed both after oral (Tambo, 1973) and inhalation (Gallaher and Loomis, 1975) administration and, in both cases, was hydrolyzed to ethanol. Gallaher and Loomis (1975) observed that, at concentrations >2000 ppm for 5 hours, endotracheally-administered ethyl acetate produced a concentration-related rise in blood ethanol levels in rats. Intraperitoneally administered ethyl acetate was hydrolyzed to ethanol, with a half-life in blood of 5-10 minutes in rats. Since in vitro half-life for conversion to ethanol in whole blood was 65-70 minutes, involvement of other enzymes in addition to blood cholinesterases was suggested. Increased blood and brain ethanol levels in rats pretreated with phenobarbital and exposed to ethyl acetate by inhalation (Diunov et al., 1983) suggests the involvement of microsomal enzymes. Pertinent data regarding ethyl acetate metabolism at lower doses and information on distribution or excretion could not be located in the available literature as cited in the Appendix.

Long-term carcinogenicity bioassays in animals could not be located in the available literature. Ethyl acetate was ineffective as a complete carcinogen in short-term skin-painting studies (Lindenfelser et al., 1974) and as an inducer of pulmonary tumors in Strain A mice (Stoner et al., 1973). Of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 11 cases were found in the group potentially exposed to 24

solvents other than benzene (Arp et al., 1983). Of these 11 cases, 3 had been exposed to ethyl acetate, among other solvents (Checkoway et al., 1984). When compared with a control group of 1350 workers, the relative risk was 5.1 ($p < 0.05$), but the multiple exposures, small sample size and lack of quantitative exposure data precluded conclusions about a causal effect. Ethyl acetate was negative for reverse mutation in *S. typhimurium* in the presence of S-9 (Ishidate et al., 1984) and in a micronucleus assay in Chinese hamsters (Basler, 1986). It did, however, induce mitotic aneuploidy in a yeast cell line (Zimmerman et al., 1985), and polyploidy and chromosomal aberrations in a mammalian cell line (Ishidate et al., 1984) in the absence of metabolic activation. There are no data on the reproductive toxicity to mammalian cells of ethyl acetate.

Rats treated by gavage with 3600 mg/kg/day ethyl acetate for 90 days had reduced food consumption and body weight gain, increased incidences of overt clinical signs of toxicity and organ weight changes including reduced absolute and relative liver and kidney weights (American Biogenics Corp. (1986). No effects were found at 900 or 300 mg/kg/day. Subchronic exposure of three guinea pigs to 2000 ppm (7206 mg/m³) ethyl acetate, 4 hours/day, 6-7 hours/week, led to no measurable changes in body weight gains, or in hematological or urinary values (Smyth and Smyth, 1928).

Oral LD₅₀ values have been listed as 5.6 g/kg (Fassett, 1963) and 10.2 g/kg (Smyth et al., 1962). Acute toxicity has been characterized by CNS and respiratory depression, circulatory abnormalities and blood dyscrasias (von Oettingen, 1960). von Oettingen (1960) described the pathology of a fatally exposed worker as respiratory tract hyperemia, petechial hemorrhaging and hemorrhagic gastritis. Mucosal irritation, narcosis and acidosis were also observed after exposure (Fassett, 1963).

An RfD of 0.9 mg/kg/day, based on a subchronic oral NOEL of 900 mg/kg/day in rats (American Biogenics Corp., 1986) using an uncertainty factor of 1000, was recently verified by U.S. EPA (1986a). An RQ of 1000 was derived based on clinical signs of CNS toxicity in female rats at the LOAEL of 3600 mg/kg/day in the study by American Biogenics Corp. (1986). Data regarding the carcinogenicity of ethyl acetate in animals and humans are inadequate; therefore, ethyl acetate is classified as a U.S. EPA Group D chemical, meaning that it is not classifiable as to its human carcinogenicity. It is worth noting that ethyl acetate is metabolized to ethanol which may present an additional health risk factor. Furthermore, ethanol is metabolized to acetaldehyde which has been shown to be carcinogenic in animal systems.

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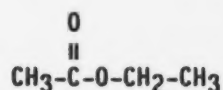
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biological oxygen demand
BODT	Biological oxygen demand test
CAS	Chemical Abstract Service
CNS	Central nervous system
DMBA	9,10-dimethyl-1,2-benzanthracene
EC ₅₀	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K _{oc}	Soil sorption coefficient standardized with respect to organic carbon
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD ₅₀	Dose lethal to 50% of recipients
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
PEL	Permissible exposure level
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
SMR	Standardized mortality ratio
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Ethyl acetate is the common chemical name for the compound also known as acetic ether; acetoxyethane; ethyl ethanoate; and acetic acid, ethyl ester. The structure, molecular weight, empirical formula and CAS Registry number for ethyl acetate are as follows:



Molecular weight: 88.10

Empirical formula: $\text{C}_4\text{H}_8\text{O}_2$

CAS Registry number: 141-78-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Ethyl acetate is a clear, colorless, volatile liquid with a characteristic fruity odor (Windholz, 1983; Verschueren, 1983). It is miscible with alcohol, acetone, chloroform and ether and soluble in water (Windholz, 1983). Selected physical properties are listed below:

Melting point:	-82 to -83.6°C	Verschueren, 1983
Boiling point:	77°C	Verschueren, 1983
Specific gravity:	0.901 (20/4°C)	Verschueren, 1983
Vapor density (air = 1.0):	3.04	Windholz, 1983
Water solubility:		
at 20°C	8.3 g/100 g	Altshuller and Everson, 1953
at 25°C	8.0 g/100 g	Altshuller and Everson, 1953
Vapor pressure:		
at 0°C	24.3 mm Hg	Ambrose et al., 1981
at 15°C	57.0 mm Hg	Ambrose et al., 1981
at 20°C	75.0 mm Hg	Ambrose et al., 1981
at 25°C	94.5 mm Hg	Ambrose et al., 1981

Log K _{ow} :	0.73	Hansch and Leo, 1985
Flash point (open cup):	7.2°C	Windholz, 1983
Autoignition temperature:	426°C	Windholz, 1983
Air conversion factors:	1 mg/m ³ = 0.28 ppm 1 ppm = 3.6 mg/m ³	

Ethyl acetate absorbs water (up to 3.3 wt. %) and is slowly decomposed by moisture, producing acetic acid and ethanol to form an acidic solution (Windholz, 1983; Tambo, 1973). It is flammable and potentially a dangerous fire and explosion risk (Hawley, 1981).

1.3. PRODUCTION DATA

The manufacturers of ethyl acetate are listed in Table 1-1 along with their respective annual capacities and production methods. In 1984, the four manufacturers listed in Table 1-1 reported production of 210.4 million pounds of ethyl acetate (USITC, 1985). Production of ethyl acetate is expected to increase at an annual rate of 2.5% through 1990 (CMR, 1986).

1.4. USE DATA

Ethyl acetate has the following use pattern (CMR, 1986):

Coating solvent	41%
Plastics solvent	8%
Miscellaneous solvent uses	13%
Chemical synthesis	2%
Export	36%

Excluding exports, ~97% of the ethyl acetate produced is used as a solvent and 3% is used in chemical synthesis.

1.5. SUMMARY

Ethyl acetate is a clear, colorless, volatile liquid with a characteristic fruity odor (Windholz, 1983; Verschueren, 1983). It is soluble in various organic solvents and in water. In 1984, the four U.S. manufacturers reported production of 210.4 million pounds of ethyl acetate (USITC, 1985).

TABLE 1-1
Ethyl Acetate Manufacturers, Capacities and Production Methods^a

Manufacturer	Location	Annual Capacity ^b (millions of pounds)	Production Method
Celanese Corporation	Pampa, TX	80	co-product of acetic acid from butane oxidation
Eastman Kodak Tennessee Eastman Texas Eastman	Kingsport, TN Longview, TX	30-35 40	esterification of acetic acid with ethanol
Monsanto Company	Springfield, MA Trenton, MI	25-30 15-20	by-product of polyvinyl butyral production from polyvinyl acetate
Union Carbide	Texas City, TX	20	by-product from acetic acid plant

^aSource: SRI, 1985; CMR, 1986

^bCapacities are for 85% ethyl acetate and are flexible.

Excluding exports, ~97% of the ethyl acetate produced is used as a solvent and 3% is used in chemical syntheses (CMR, 1986). About 64% of solvent use involves coating applications (CMR, 1986).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. The hydrolysis half-life of ethyl acetate at pH 7 and 25°C has been reported to be 2.0 years (Mabey and Mill, 1978). Based on the acid, neutral and base hydrolysis rate constants reported by Mabey and Mill (1978) at 25°C, the compound will not significantly hydrolyze at pH ≤ 6 , but the hydrolysis half-lives at pH 8 and 9 are estimated to be 73 days and 7.3 days, respectively. Therefore, hydrolysis will not be an important removal mechanism in neutral or acidic bodies of water; however, hydrolysis may become increasingly important as the pH of the water increases above pH 7.

2.1.2. Oxidation. The rate constant for the reaction of ethyl acetate with HO radical in aqueous solution at room temperature has been reported to be $2.4 \times 10^8 \text{ M}^{-1} \text{ sec}^{-1}$ (Anbar and Neta, 1967; Dorfman and Adams, 1973). Assuming that the HO radical concentration in sunlit natural water is $\sim 10^{-17} \text{ M}$ (Mill and Mabey, 1985), the half-life for this reaction is calculated to be 9.15 years, which is not environmentally significant.

2.1.3. Photolysis. Pertinent data regarding the photolysis of the ethyl acetate could not be located in the available literature as cited in the Appendix.

2.1.4. Microbial Degradation. A number of BOD studies (5- to 20-day incubation periods; concentrations of ethyl acetate ranging from 0.05-1000 ppm) using activated sludge and sewage inocula have demonstrated that ethyl acetate is readily biodegradable (Lamb and Jenkins, 1952; Young et al., 1968; Ettinger, 1956; Heukelekian and Rand, 1955; Heukelekian and Gellman, 1951; Price et al., 1974; Takemoto et al., 1981; Freitag et al., 1984). Stover and Kincannon (1983) found ethyl acetate to be readily biodegradable at concentrations of 247-278 ppm in a bench-scale, continuous-flow activated

sludge reactor. Thom and Agg (1975) reported that ethyl acetate is generally easily biodegradable by biological sewage treatment.

Lamb and Jenkins (1952) conducted standard BOD tests with ethyl acetate (2.5 ppm) using river water as inoculum, the BODT observed for 5, 10 and 20 days was 11.0, 59.4 and 66.0%, respectively. This is indicative of significant biodegradation and a biodegradation half-life of <10 days in natural water.

Ethyl acetate has also been shown to biodegrade under anaerobic conditions (Chou et al., 1979; Shelton and Tiedje, 1984). The above data suggest that microbial degradation may significantly contribute to the removal of ethyl acetate from natural waters and sediments.

2.1.5. Volatilization. The equilibrium ratio of ethyl acetate in the vapor-phase to ethyl acetate in dilute aqueous solution at 25°C has been experimentally measured to be 5.4×10^{-3} (Hine and Mookerjee, 1975; Wolfenden, 1976). This corresponds to a Henry's Law constant of 1.3×10^{-4} atm-m³/mol, which indicates that volatilization may be significant from all bodies of water, although it may not be rapid (Lyman et al., 1982). Based on the method of Lyman et al. (1982), the volatilization half-life of ethyl acetate from a river 1 m deep flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec is estimated to be ~9 hours.

2.1.6. Adsorption. Experimental aqueous adsorption data could not be located in the available literature as cited in the Appendix. Based on a relatively low log K_{ow} value of 0.73 (Hansch and Leo, 1985) and a high WS of 80 g/g at 25°C (Altshuller and Everson, 1953), ethyl acetate is not expected to significantly partition from the water column to sediments.

2.1.7. Bioconcentration. BCFs can be estimated from the following recommended equations (Lyman et al., 1982):

$$\log \text{BCF} = 0.76 \log K_{ow} - 0.23 \quad (2-1)$$

$$\log \text{BCF} = 2.791 - 0.564 \log \text{WS (in ppm)} \quad (2-2)$$

Based on a $\log K_{ow}$ value of 0.73 (Hansch and Leo, 1985) and WS of 80,000 ppm at 25°C (Altshuller and Everson, 1953), the BCF values calculated from Equations 2-1 and 2-2 are 2 and 1, respectively. These BCF values indicate that significant bioconcentration in aquatic organisms is not expected to occur.

2.2. AIR

The rate constants for the vapor-phase reaction between ethyl acetate and photochemically produced HO radical in the atmosphere have been experimentally measured to be 1.82×10^{-12} cm³/molecule-sec at 19°C and 1.7×10^{-12} cm³/molecule-sec at 23°C (Atkinson, 1985). Assuming an average ambient atmospheric concentration of 8×10^5 HO radical/cm³, the half-life for this reaction is estimated to be 5.5-5.9 days. The reaction between ethyl acetate and HO radical proceeds by hydrogen atom abstraction at the alkoxy end of the ethyl acetate molecule (Campbell and Parkinson, 1978). Under photochemical smog conditions, the concentration of HO radical in the smog may be 1 order of magnitude higher than normal atmospheric conditions, and the removal of ethyl acetate through HO radical reaction will be significant (Campbell and Parkinson, 1978).

2.3. SOIL

2.3.1. Microbial Degradation. Although soil microbial degradation studies could not be located in the available literature as cited in the Appendix, the ability of ethyl acetate to readily biodegrade in activated sludges, sewage and natural river water (see Section 2.1.4.) suggests that biodegradation by soil microflora is likely to occur.

2.3.2. Leaching. Experimental soil leaching data could not be located in the available literature as cited in the Appendix. The relatively high WS (80 g/l at 25°C) (Atshuller and Everson, 1953) and low log K_{ow} value (0.73) (Hansch and Leo, 1985) of ethyl acetate suggest that significant leaching may occur in many types of soil.

2.3.3. Volatilization. Ethyl acetate is classified as a rapidly evaporating solvent (Davis, 1966); the evaporation half-life of a thin film from a glass surface at 25°C and 0-5% relative humidity is 56 seconds. This would suggest that evaporation from dry soil surfaces is likely to occur quite rapidly. Since ethyl acetate also volatilizes from water (see Section 2.1.5.), evaporation from moist soil surfaces may also occur.

2.4. SUMMARY

When released to water, microbial degradation and volatilization are likely to be important removal mechanisms. Ethyl acetate has been shown to be readily biodegradable in a number of BOD studies (using activated sludge and sewage), in a natural water BOD test and under anaerobic conditions (Stover and Kincannon, 1983; Price et al., 1974; Thom and Agg, 1975). The volatilization half-life from a river 1 m deep flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec has been estimated to be ~9 hours from the experimentally measured vapor-aqueous solution equilibrium ratio (Hine and Mookerjee, 1975). Hydrolysis will not be important in neutral or acidic water, but may become significant in alkaline water; the respective hydrolysis half-lives at 25°C and pHs 7, 8 and 9 are 2.0 years, 73 days and 7.3 days (Mabey and Mill, 1978). Aquatic oxidation (by HO radical), adsorption to sediment, and bioconcentration are not expected to be important (Anbar and Neta, 1967). If released to the atmosphere, ethyl acetate will react with photochemically produced HO radical with an estimated half-life of

5.5-5.9 days at 19-23°C (Atkinson, 1985). If released to soil, ethyl acetate is likely to be susceptible to significant leaching and biodegradation. Volatilization from dry surfaces is expected to be relatively rapid.

3. EXPOSURE

3.1. WATER

Ethyl acetate has been qualitatively detected in drinking water from New Orleans (Keith et al., 1976), Kitakyushu, Japan (Akiyama et al., 1980), and various drinking water supplies in Great Britain (Fielding et al., 1981). It was qualitatively identified in only 1/204 surface water sites sampled near heavily industrialized areas across the United States (Ewing et al., 1977) and in 1/30 samples collected from the Delaware River (Dewalle and Chian, 1978). Concentrations ranging from 60-585 ppb were found in the Hayashida River in Japan (Yasuhara et al., 1981).

Ellis et al. (1982) qualitatively identified ethyl acetate in a secondary wastewater effluent from a petroleum refinery in Lockport, IL. It was also found in finished water from an "advanced waste treatment" plant in Lake Tahoe, CA (U.S. EPA, 1984) and in effluents from sewage treatment plants (U.S. EPA, 1976). Sabel and Clark (1984) detected ethyl acetate at concentrations of 13-290 ppb in leachates from municipal solid waste landfills and at concentrations of 14-24 ppb in groundwaters adjacent to the landfills in Minnesota.

Wastewaters resulting from the industrial production and use of ethyl acetate are a potential source of exposure of the compound to the aquatic environment, although biological treatment is normally effective in removing ethyl acetate from contaminated wastewater (see Section 2.1.4.). Ethyl acetate is a naturally occurring compound and has been detected in volatile emissions from plant tissues (Nicholas, 1973) and from microbes and animal waste (Graedel, 1978). Therefore, its presence in some natural waters may be a result of natural processes.

3.2. FOOD

Ethyl acetate is an ester component of U.S.-produced lager beer, formed as a result of the reaction of acetyl coenzyme A with ethanol (Reed, 1984). Lager beer usually contains an ester concentration of 25-50 ppm; however, top-fermented beers may contain higher amounts of ethyl acetate (Reed, 1984). Ethyl acetate is also a component in vinegar (Webb, 1983; Rogers and Fischetti, 1980) and a volatile component of roasted filbert nuts (Kinlin et al., 1972). Small amounts of ethyl acetate may be added to carbonated grape beverages to increase the aroma (Jones, 1978). Pellizzari et al. (1982) detected ethyl acetate in 1/12 samples of human milk.

3.3. INHALATION

Ethyl acetate was qualitatively detected in the ambient atmosphere of the Los Angeles Basin and in Houston, TX (Pellizzari et al., 1976), in the ambient air of Leningrad, Soviet Union (Ioffe et al., 1977), in the urban air of Tuscaloosa, AL, and in the rural air of the Talladega National Forest (Holzer et al., 1977). Isidorov et al. (1985) concluded that ethyl acetate is a volatile component emitted by Scotch pine trees, which suggests that its presence in forest atmospheres may partly be of natural origin. Nicholas (1973) also reported that ethyl acetate is a volatile plant product.

Carter and Linsky (1974) identified ethyl acetate in atmospheric emissions from whiskey fermentation units. Pellizzari (1982) found ethyl acetate concentrations ranging from trace-230 $\mu\text{g}/\text{m}^3$ in the ambient air surrounding an industrial waste disposal site near Edison, NJ. Household solid waste stored under anaerobic conditions (Kamiya and Ose, 1981) and volatile components of fermented eggs (Bullard et al., 1978) were found to emit ethyl acetate. Contaminated beef emitted ethyl acetate as a result of microbial growth (Dainty et al., 1985). Ethyl acetate has been identified in tobacco smoke (Schumacher et al., 1977; Holzer et al., 1976).

Krotoszynski et al. (1979) monitored the expired air of a selected urban population of normal, healthy, nonsmoking human subjects. Ethyl acetate was detected in 13.7% of 387 expired air samples from 54 human subjects at a geometric mean concentration of 0.447 ng/l. Conkle et al. (1975) found levels of none detected to 190.0 µg/hour in human expired air.

Ethyl acetate is predominantly used as a solvent, particularly by the coatings industry (see Section 1.4.). Ethyl acetate evaporates during this coating solvent use, which is probably the greatest man-made source of exposure to ethyl acetate in the atmosphere. According to NIOSH (1984), as many as 2.2 million U.S. workers are potentially exposed to ethyl acetate.

3.4. DERMAL

Pertinent dermal monitoring data could not be located in the available literature as cited in the Appendix. Dermal exposure, particularly occupational, is likely from its solvent use in different industries.

3.5. SUMMARY

Ethyl acetate has been qualitatively detected in drinking water (Keith et al., 1976; Akiyama et al., 1980; Fielding et al., 1981), surface water (Ewing et al., 1977; Dewalle and Chian, 1978; Yasuhara et al., 1981), wastewater effluents (Ellis et al., 1982; U.S. EPA, 1984) and leachate/groundwater from landfills (Sabel and Clark, 1984). It is a small volume component of beer (Reed, 1984) and vinegar (Webb, 1983; Rogers and Fischetti, 1980) and has been found in human breast milk (Pellizzari et al., 1982). It has been identified in urban ambient air (Pellizzari et al., 1976; Ioffe et al., 1977; Holzer et al., 1977) and in the ambient rural air of a U.S. national forest (Holzer et al., 1977). Evaporation of ethyl acetate used as a solvent is probably the greatest man-made source of exposure to the

compound in the atmosphere. Ethyl acetate is also a naturally occurring compound; it was detected in volatile emissions from plants and trees (Nicholas, 1973; Isidorov et al., 1985), microbes and animal waste (Graedel, 1978). It is emitted from contaminated beef as a result of microbial growth (Dainty et al., 1985), from stored household wastes (Kamiya and Ose, 1981) and from fermented eggs (Bullard et al., 1978). Emissions from whiskey fermentation contain ethyl acetate (Carter and Linsky, 1974), and it has also been identified in tobacco smoke (Schumacher et al., 1977; Holzer et al., 1976), and in exhaled air from normal humans (Conkle et al., 1975; Krotoszynski et al., 1979).

4. PHARMACOKINETICS

4.1. ABSORPTION

Quantitative data regarding the absorption of ethyl acetate could not be located in the available literature; however, Tambo (1973) reported that oral administration of unspecified doses of ethyl acetate in rabbits resulted in "drunkenness" and acidosis, indicating that ethyl acetate or its hydrolysis products, ethanol and acetic acid, was absorbed through the gastrointestinal tract.

In anesthetized (pentobarbital) rats administered >2000 ppm ethyl acetate (>7206 mg/m³) by an endotracheal tube for 5 hours, accumulation of ethanol in the blood suggested absorption through the respiratory system (Gallaher and Loomis, 1975).

4.2. DISTRIBUTION

Pertinent data regarding the distribution of ethyl acetate could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Oral administration of ethyl acetate to rabbits led to the accumulation of blood ethanol and depression of blood pH, presumably due to the release of acetic acid (Tambo, 1973). Similarly, endotracheal administration of concentrations >2000 ppm ethyl acetate (>7206 mg/m³) for 5 hours in rats led to a concentration-related increase in blood ethanol levels (Gallaher and Loomis, 1975). The authors concluded that, at >2000 ppm, the absorption rate of ethyl acetate exceeded the rate of metabolism of ethanol.

Gallaher and Loomis (1975) intraperitoneally injected four Sprague-Dawley rats with 1.6 mL/kg of ethyl acetate. Blood samples were taken at selected time points, from ~5 minutes to 3 hours postinjection. Blood ethanol concentrations peaked at ~15 minutes after injection, then decreased slowly. The half-life of ethyl acetate in blood in vivo was calculated to

be 5-10 minutes; accumulation was negligible. In an in vitro assay in whole blood from rats, incubation with ethyl acetate led to a simple stoichiometric hydrolysis to ethanol. The half-life for this in vitro reaction was calculated to be 65-70 minutes. Gallaher and Loomis (1975), therefore, proposed that nonspecific cholinesterases and pseudocholinesterases were probably involved in the in vivo hydrolysis reaction but were not solely responsible.

Diunov et al. (1983) observed that pretreatment with phenobarbital increased blood and brain levels of both ethyl acetate and its major metabolite, ethanol, in rats anesthetized by inhalation with ethyl acetate. This finding suggests that microsomal enzymes are involved in the hydrolysis of ethyl acetate.

4.4. EXCRETION

Pertinent data regarding the excretion of ethyl acetate could not be located in the available literature as cited in the Appendix.

4.5. SUMMARY

Ethyl acetate was absorbed both after oral (Tambo, 1973) and inhalation (Gallaher and Loomis, 1975) administration and, in both cases, was hydrolyzed to ethanol. Gallaher and Loomis (1975) observed that, at concentrations >2000 ppm for 5 hours, endotracheally-administered ethyl acetate produced a concentration-related rise in blood ethanol levels in rats. Ethyl acetate intraperitoneally administered to rats was hydrolyzed to ethanol, with a half-life in blood of 5-10 minutes. Since the in vitro half-life for conversion to ethanol in whole blood was 65-70 minutes, involvement of other enzymes in addition to blood cholinesterase was suggested. Increased blood and brain ethanol levels in rats pretreated with phenobarbital and exposed to ethyl acetate by inhalation (Diunov et al.,

1983) suggests the involvement of microsomal enzymes. Pertinent data regarding ethyl acetate metabolism at lower doses and information on distribution or excretion could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

In a retrospective cohort study, McMichael et al. (1975) reported an excess of lymphocytic leukemias in 40- to 84-year-old active and retired male workers in a rubber industry plant in Akron, OH. The entire cohort of 6678 employees, with an average length of employment of 25 years, was studied for 9 years. SMRs were calculated using the U.S. male age-specific death rates for a year within the 9-year study period. The cohort was divided into groups with ages of 40-64 and 65-84. Statistically significant elevated rates of death from several types of cancers were observed, particularly of the lymphatic and hematopoietic systems. In the 40- to 64-year age group, there were 11 cases of death from leukemia compared with 3.5 expected (SMR=314). There were four deaths from leukemia in the 65- to 84-year age group; the expected number was not reported, but the SMR was ~40. For lymphosarcomas, reticulum cell sarcomas and Hodgkin's Disease, there were 16 deaths observed compared with 6.2 expected (SMR=258) for the full age range of 40-84 years.

When mortality data from the individual hematopoietic cancers were analyzed separately, SMRs of 764 for lymphatic leukemia (eight cases) and 205 for myeloid leukemia (three cases) were calculated for the 40- to 64-year age group. The SMR for Hodgkin's Disease (four cases) was ~330 for the 65- to 84-year age group.

McMichael et al. (1975) also reported a case-control study that revealed a statistically significant positive association between exposure to organic solvents and leukemia; however, they did not associate the leukemia with specific solvents. Subsequently, Arp et al. (1983) estimated the worker exposure to benzene and other unspecified solvents from the records of this

Akron, OH, rubber company. Of the 15 cases of leukemia noted in the McMichael et al. (1975) study, 11 cases of leukemia were found in the group exposed to other solvents. Compared with matched case-controls, the relative risk was 4.5 ($p=0.08$). Checkoway et al. (1984) determined 24 solvents to which the 11 other solvent-exposed leukemia cases had been exposed, including ethyl acetate. Exposure to a specific chemical was defined as >12 months cumulative duration of employment in the particular solvent-related department. Of the 11 cases, 3 had been exposed to ethyl acetate by this definition, which does not exclude exposure to the other 23 solvents. Controls consisted of a 20% age-stratified random sample of the cohort (1350 workers). The relative risk associated with ethyl acetate by this analysis was 5.1 ($p<0.05$). The multiple exposures, small sample size and lack of quantitative exposure data precludes conclusions about a causal effect of ethyl acetate or any other solvents.

Ethyl acetate was tested as a complete carcinogen in eight female CD-1 mice given 0.2 ml ethyl acetate, on the shaved back, 45 times over 23 weeks (Lindenfelser et al., 1974). None of the mice developed papillomas. Stoner et al. (1973) gave 3.6 or 18 g/kg ethyl acetate in tricaprylin intraperitoneally to 15 male and 15 female strain A/He mice, 3 times/week for a total of 24 doses. The mice were sacrificed 24 weeks after the first dose and the lungs were examined grossly and microscopically. No compound-related increases in lung tumors or other pathologies were observed over tricaprylin-treated controls.

5.2. MUTAGENICITY

As indicated in Table 5-1, ethyl acetate was not mutagenic against any of six strains of Salmonella typhimurium in reverse mutation testing, in the presence of rat microsomal protein (Ishidate et al., 1984). It increased

TABLE 5-1
Mutagenicity Testing of Ethyl Acetate

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comments	Reference
Reverse mutation	<u>Salmonella</u> <u>typhimurium</u> TA92, TA94, TA98, TA100 TA1535, TA1537	99.9% pure in DMSO	plate incorporation	50 mg/plate	+S-9	-	Listed concentration is the highest non- cytotoxic one; ethyl acetate was not tested in the absence of S-9	Ishidate et al., 1984
Mitotic aneuploidy	<u>Saccharomyces</u> <u>cerevisiae</u> D61.M	>97% pure	plated onto a growing culture	2.44%	NR	+	Negative for point mutation and recombina- tion	Zimmermann et al., 1985
Chromosomal aberrations	Chinese hamster lung fibroblasts	99.9% pure in ethanol	liquid suspension	9.0 mg/ml	none	+	Increased incidences of polyploidy and structural chromosomal aberrations at highest nontoxic dose	Ishidate et al., 1984
Micronuclei	Chinese hamsters	NR	corn oil suspension	473 mg/kg i.p. 2500 mg/kg p.o.		-	Negative results	Basler, 1986

NR = Not reported

the incidence of mitotic aneuploidy, but not point mutations or recombinations, in Saccharomyces cerevisiae strain D61.M (Zimmermann et al., 1985). Studies by Groschel-Stewart et al. (1985) showed that ethyl acetate inhibited the assembly of procine brain tubulin in vitro. These data led Groschel-Stewart and co-workers to propose that ethyl acetate interacts with tubulin, not DNA, in causing chromosomal malsegregation in yeast. Ishidate et al. (1984) also observed increased frequencies of polyploidy and structural chromosomal aberrations in a Chinese hamster lung fibroblast line treated with ethyl acetate. However, whether ethyl acetate can produce numerical and structural chromosomal abnormalities in intact mammals is problematic. Basler (1986) injected Chinese hamsters intraperitoneally (473 mg/kg) and exposed animals per os (2500 mg/kg) with ethyl acetate and reported negative results in micronucleus test. Micronuclei formation can be the result of chromosomal malsegregation or clastogenicity.

5.3. TERATOGENICITY

There were no data located in the available literature regarding the structural effects of ethyl acetate on developing mammalian organisms. Verrett et al. (1980) administered 25 mg ethyl acetate/egg into white Leghorn chicken eggs by either the yolk sack or into the air cell, at one of two stages of incubation. No fetal abnormalities were encountered.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of ethyl acetate could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

There were no data located in the available literature concerning the chronic exposure of experimental animals to ethyl acetate.

American Biogenics Corp. (1986) conducted a subchronic oral study using Sprague-Dawley rats. Groups of 30 male and 30 female rats were treated by gavage with ethyl acetate (99.9% pure) in corn oil at doses of 0, 300, 900 or 3600 mg/kg/day for up to 93 days. An interim kill of 10 rats/sex/group was performed on days 44 and 45, while the remaining rats were killed on days 91, 92 or 93. The rats were examined for mortality, morbidity, overt clinical signs, body weight gain and food consumption. Hematology, clinical chemistry and urinalysis parameters were monitored, and ophthalmological examinations were performed before the interim and final sacrifices. All rats that died during the study and that were sacrificed were necropsied and examined for gross lesions, and major organs were weighed. Comprehensive histological examination was performed on all control and high-dose rats that died or that were killed at the terminal sacrifice. Histological examination of low- and middle-dose rats that died or were killed at the terminal sacrifice was limited to the heart, kidneys, liver and gross lesions. There were no deaths in the control or 300 mg/kg/day groups, but 2/30 rats at 900 mg/kg/day and 7/30 rats at 3600 mg/kg/day died before the scheduled sacrifice. The deaths of several high-dose rats were due to pulmonary accident or gavaging trauma. High-dose males had treatment-related significantly reduced body weight gain and high-dose males and females had significantly increased incidences of salivation, irregular breathing and lethargy compared with controls. Results of clinical studies and ophthalmological, gross and histological examinations were unremarkable. Statistically significant organ weight changes occurred in high-dose rats and consisted of decreased absolute spleen weight, absolute and relative (to brain) kidney weights, absolute and relative (to body and brain) liver weights, and increased relative testes (to body) weight in males and a decreased liver-to-body weight ratio in females.

In a subchronic inhalation study, Smyth and Smyth (1928) exposed three guinea pigs of unspecified sex and strain to 2000 ppm (7206 mg/m³) ethyl acetate vapors for 65 exposures. Daily inhalation exposures for the first 2 weeks were for unspecified lengths of time; subsequent exposures were for 4 hours/day, 6 days/week. The guinea pigs were weighed approximately weekly, and blood counts and urinalyses were performed every 2 weeks. Three control guinea pigs were exposed to room air. There were no exposure-related effects on body weight gain or on hematological or urinary parameters.

5.6. OTHER RELEVANT INFORMATION

Oral LD₅₀ values for ethyl acetate in rats were given as 5.6 g/kg (Fassett, 1963) and 10.2 g/kg (Smyth et al., 1962). Fassett (1963) also defined an 8-hour inhalation LC₅₀ of 1600 ppm (5765 mg/m³) in rats. Smyth et al. (1962) found that six male albino rats could survive a 4-hour exposure to 8000 ppm (~29,000 mg/m³) ethyl acetate, but that a 16,000 ppm (~58,000 mg/m³) concentration was fatal to all rats. These investigators determined that the dermal LD₅₀ in rabbits was >20 ml/kg. Smyth et al. (1962) stated that ethyl acetate was only mildly irritating to the rabbit cornea; however, the insensitivity of the cornea model was demonstrated by Sommer (1957), who repeatedly exposed rabbits to the same vapor concentrations that were highly irritating to workers, with no evidence of corneal damage to the experimental animals.

von Oettingen (1960) described the acute effects of ethyl acetate as CNS depression, circulatory aberrations, erythrocytosis, neutrophilia, lymphopenia and altered respiratory rates. In a worker fatally poisoned by ethyl acetate vapor, pathology was characterized by respiratory tract hyperemia, petechial hemorrhages of the epicardium and pleura and hemorrhagic gastritis (von Oettingen, 1960). Fassett (1963) described the acute effects of

saturated aliphatic ester exposure in man as similar to those in animals, including mucosal irritation and gradual narcosis, and acidosis, probably as a result of the hydrolysis reaction. Fassett (1963) observed no anesthetic effects in man, as is often seen after chlorinated hydrocarbon exposure, after exposure to 400-600 ppm (1441-2162 mg/m³) ethyl acetate.

5.7. SUMMARY

Long-term carcinogenicity bioassays in animals could not be located in the available literature. Ethyl acetate was ineffective as a complete carcinogen in short-term skin-painting studies (Lindenfelser et al., 1974) and as an inducer of pulmonary tumors in strain A mice (Stoner et al., 1973). Of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 11 cases were found in the group potentially exposed to 24 solvents other than benzene (Arp et al., 1983). Of these 11 cases, 3 had been exposed to ethyl acetate, among other solvents (Checkoway et al., 1984). When compared with a control group of 1350 workers, the relative risk was 5.1 ($p < 0.05$), but the multiple exposures, small sample size and lack of quantitative exposure data precluded conclusions about a causal effect. Ethyl acetate was negative for reverse mutation in S. typhimurium in the presence of S-9 (Ishidate et al., 1984) and in a micronucleus assay in mice (Hayashi et al., 1981). It did, however, induce aneuploidy in a yeast cell line (Zimmerman et al., 1985), and polyploidy and chromosomal aberrations in a mammalian cell line (Ishidate et al., 1984) in the absence of metabolic activation. There are no data on the reproductive toxicity to mammalian cells of ethyl acetate.

Rats treated by gavage with 3600 mg/kg/day ethyl acetate for 90 days had reduced food consumption and body weight gain, increased incidences of overt clinical signs of toxicity and organ weight changes including reduced

absolute and relative liver and kidney weights (American Biogenics Corp., 1986). No effects were found at 900 or 300 mg/kg/day. Subchronic exposure of three guinea pigs to 2000 ppm (7206 mg/m³) ethyl acetate, 4 hours/day, 6-7 hours/week, led to no measurable changes in body weight gains, or in hematological or urinary values (Smyth and Smyth, 1928).

Oral LD₅₀ values have been listed as 5.6 g/kg (Fassett, 1963) and 10.2 g/kg (Smyth et al., 1962). Acute toxicity has been characterized by CNS and respiratory depression, circulatory abnormalities and blood dyscrasias (von Oettingen, 1960). von Oettingen (1960) described the pathology of a fatally exposed worker as respiratory tract hyperemia, petechial hemorrhaging and hemorrhagic gastritis. Mucosal irritation, narcosis and acidosis were also observed after exposure (Fassett, 1963).

6. AQUATIC TOXICITY

6.1. ACUTE

Data concerning the acute toxicity of ethyl acetate to aquatic vertebrates are presented in Table 6-1. The lowest reported LC_{50} value is 125 mg/l (48-hour) for medaka, Oryzias latipes (Slooff et al., 1983). The lowest reported toxic concentration in acute exposures was 19.4 mg/l, which inhibited growth but did not affect the survival of fathead minnows, Pimephales promelas (Barron and Adelman, 1984). The amphibian species tested appeared to be about as sensitive to ethyl acetate as the fish species (see Table 6-1).

Data concerning the acute toxicity of ethyl acetate to aquatic invertebrates are presented in Table 6-2. The most sensitive species tested was the stonefly, Nemoura cinerea, with a 48-hour LC_{50} value of 130 mg/l (Slooff, 1983). No lethal concentrations <100 mg/l were reported for fish or invertebrates (see Tables 6-1 and 6-2).

6.2. CHRONIC

In a 32-day embryo-larval bioassay, growth of fathead minnows was inhibited at 9.65 mg/l, the lowest concentration tested (Barron and Adelman, 1984).

6.3. PLANTS

The available data concerning the effects of ethyl acetate on aquatic plants and bacteria are presented in Table 6-3. Scenedesmus quadricauda and S. pannonicus were by far the most sensitive species, each having a toxicity threshold for inhibition of cell multiplication of 15 mg/l (Bringmann and Kuehn, 1978; Slooff et al., 1983).

6.4. RESIDUES

Geyer et al. (1984) reported a 24-hour BCF of 13,500 for algae, Chlorella fusca, exposed to ethyl acetate.

TABLE 6-1

Acute Toxicity of Ethyl Acetate to Fish and Amphibians

Species	Concentration (mg/L)	Effect	Reference
FISH			
Rainbow trout, <u>Salmo gairdneri</u>	260 240 230	48-hour LC ₅₀ 48-hour NOEC 96-hour LC ₅₀	Slooff et al., 1983 Slooff et al., 1983 McKim et al., 1985
Fathead minnow, <u>Pimephales promelas</u>	270 180 19.4	48-hour LC ₅₀ 48-hour NOEC 96-hours, decreased growth, no effect on survival	Slooff et al., 1983 Slooff et al., 1983 Barron and Adelman, 1984
Golden orfe, <u>Leuciscus idus</u>	270 270-333 135-306	48-hour LC ₅₀ 48-hour LC ₅₀ 48-hour LC ₀	Slooff et al., 1983 Juhnke and Ludemann, 1978 Juhnke and Ludemann, 1978
Medaka, <u>Oryzias latipes</u>	125 100	48-hour LC ₅₀ 48-hour NOEC	Slooff et al., 1983 Slooff et al., 1983
Guppy, <u>Poecilia reticulata</u>	210 160	48-hour LC ₅₀ 48-hour NOEC	Slooff et al., 1983 Slooff et al., 1983
Bluegill, <u>Lepomis macrochirus</u>	100	96-hour LC ₀	Buzzell et al., 1968
Indian catfish, <u>Heteropneustes fossilis</u>	212.5 63.89 170	96-hour LC ₅₀ 96-hour safe concentration, impaired carbohydrate metabolism	Gupta and Srivastava, 1982 Gupta and Srivastava, 1982 Gupta and Srivastava, 1982

TABLE 6-1 (cont.)

Species	Concentration (mg/g)	Effect	Reference
AMPHIBIANS			
Clawed toad, <u>Xenopus laevis</u>	180 100	48-hour LC ₅₀ 48-hour NOEC	Slooff et al., 1983 Slooff et al., 1983
Mexican axolotl, <u>Ambystoma mexicanum</u>	145 100	48-hour LC ₅₀ 48-hour NOEC	Slooff et al., 1983 Slooff et al., 1983
Frog, <u>Rana pipiens</u>	2643-3172	threshold narcotic concen- tration	Munch, 1972

TABLE 6-2

Acute Toxicity of Ethyl Acetate to Aquatic Invertebrates

Species	Concentration (mg/L)	Effect	Reference
CRUSTACEANS			
Water flea, <u>Daphnia magna</u>	590	48-hour LC ₅₀	Slooff et al., 1983
	370	48-hour NOEC	Slooff et al., 1983
	2500	24-hour LC ₅₀	Bringmann and Kuehn, 1977
	625	24-hour LC ₀	Bringmann and Kuehn, 1977
	5000	24-hour LC ₁₀₀	Bringmann and Kuehn, 1977
	3090	24-hour EC ₅₀ , immobilization	Bringmann and Kuehn, 1982
	717	48-hour LC ₅₀	Canton and Adema, 1978
Water flea, <u>Daphnia pulex</u>	262	48-hour LC ₅₀	Canton and Adema, 1978
	103	48-hour NOEC	Slooff et al., 1983
Water flea, <u>Daphnia cucullata</u>	164	48-hour LC ₅₀	Canton and Adema, 1978
Brine shrimp, <u>Artemia salina</u>	1590	24-hour LC ₅₀	Price et al., 1974
	346-645	EC ₅₀ , immobilization	Foster and Tullis, 1985
Amphipod, <u>Gammarus pulex</u>	750	48-hour LC ₅₀	Slooff, 1983
Isopod, <u>Asellus aquaticus</u>	1600	48-hour LC ₅₀	Slooff, 1983
INSECTS			
Mayfly, <u>Cloeon dipterum</u>	480	48-hour LC ₅₀	Slooff, 1983
Stonefly, <u>Nemoura cinerea</u>	130	48-hour LC ₅₀	Slooff, 1983
Dragonfly, <u>Ischnura elegans</u>	600	48-hour LC ₅₀	Slooff, 1983

TABLE 6-2 (cont.)

Species	Concentration (mg/l)	Effect	Reference
INSECTS (cont.)			
Water boatman, <u>Corixa punctata</u>	600	48-hour LC ₅₀	Slooff, 1983
Midge, <u>Chironomus</u> gr. <u>thummi</u>	750	48-hour LC ₅₀	Slooff, 1983
Mosquito, <u>Aedes aegypti</u>	350	48-hour LC ₅₀	Slooff et al., 1983
	160	48-hour NOEC	Slooff et al., 1983
	7400	4-hour LC ₅₀	Kramer et al., 1983
Mosquito, <u>Culex pipiens</u>	3950	48-hour LC ₅₀	Slooff et al., 1983
	2400	48-hour NOEC	Slooff et al., 1983
MOLLUSKS			
Snail, <u>Lymnaea stagnalis</u>	1100	48-hour LC ₅₀	Slooff et al., 1983
	560	48-hour NOEC	Slooff et al., 1983
ANNELIDS			
Oligochaete, Tubificidae	760	48-hour LC ₅₀	Slooff, 1983
Leech, <u>Erpobdella octoculata</u>	1200	48-hour LC ₅₀	Slooff, 1983
PROTOZOA			
Flagellate, <u>Entosiphon sulcatum</u>	202	toxicity threshold	Bringmann and Kuehn, 1981
	890	toxicity threshold	Slooff et al., 1983
Flagellate, <u>Chilomonas paramecium</u>	3250	toxicity threshold	Bringmann and Kuehn, 1981
Ciliate, <u>Uronema parduczi</u>	1020	toxicity threshold	Bringmann and Kuehn, 1981

TABLE 6-2 (cont.)

Species	Concentration (mg/L)	Effect	Reference
MISCELLANEOUS			
Flatworm, <u>Dugesia lugubris</u>	3020	48-hour LC ₅₀	Slooff, 1983
Hydra, <u>Hydra oligactis</u>	1350	48-hour LC ₅₀	Slooff et al., 1983
	1120	48-hour NOEC	Slooff et al., 1983

TABLE 6-3
Effects of Ethyl Acetate in Aquatic Plants and Bacteria

Species	Concentration (mg/l)	Effect	Reference
BACTERIA			
<u>Pseudomonas putida</u>	650	toxicity threshold	Bringmann and Kuehn, 1980
<u>Photobacterium phosphoreum</u>	5870	15-minute EC ₅₀ , decreased light production	DeZwart and Slooff, 1983
BLUE-GREEN ALGAE			
<u>Microcystis aeruginosa</u>	550	toxicity threshold	Bringmann and Kuehn, 1978
GREEN ALGAE			
<u>Scenedesmus quadricauda</u>	15	toxicity threshold	Bringmann and Kuehn, 1978
<u>Scenedesmus pannonicus</u>	15	toxicity threshold	Slooff et al., 1983
<u>Chlorella pyrenoidosa</u>	1000	NOEC	Slooff et al., 1983
<u>Selenastrum capricornutum</u>	2000	NOEC	Slooff et al., 1983
<u>Selenastrum sp.</u>	2500	96-hour EC ₅₀	Slooff, 1982

6.5. SUMMARY

LC₅₀ values of 125-270 mg/l were reported for various fish and amphibian species (see Table 6-1), with medaka, Oryzias latipes, having the lowest LC₅₀ (Slooff et al., 1983). LC₅₀ values of 130-3950 mg/l were reported for various invertebrates, with the stonefly, Nemoura cinerea, having the lowest value (Slooff, 1983). The lowest reported acutely toxic concentration for fish or invertebrates was 19.4 mg/l, which inhibited growth of fathead minnows in a 96-hour exposure (Barron and Adelman, 1984). The only chronic toxicity data were provided by a 32-day fathead minnow embryo-larval bioassay in which growth was impaired at concentrations of ≥ 9.65 mg/l (Barron and Adelman, 1984). Among aquatic plants and bacteria, Scenedesmus sp. were by far the most sensitive, having a threshold for inhibition of cell multiplication of 15 mg/l (Bringmann and Kuehn, 1978; Slooff et al., 1983).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1985-1986) listed a TLV-TWA of 400 ppm (~1400 mg/m³) for 8-hour occupational exposure to ethyl acetate. The ACGIH (1986) reported that the stated TLV-TWA should provide for a large overall health safety factor, but may allow for mild irritation to workers unaccustomed to exposure. These conclusions appeared to be based on limited evidence from human occupational exposure studies. The OSHA (1985) PEL is 200 ppm, or ~610 mg/m³.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of ethyl acetate could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Long-term carcinogenicity bioassays of ethyl acetate in animals could not be located in the available literature as cited in the Appendix. Ethyl acetate was ineffective as a complete carcinogen in short-term skin-painting studies (Lindenfelser et al., 1974) and as an inducer of pulmonary tumors in strain A mice (Stoner et al., 1973). Of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 11 cases were found in the group potentially exposed to at least 24 solvents other than benzene (Arp et al., 1983). Of these 11 cases, 3 had been exposed to ethyl acetate, among other solvents (Checkoway et al., 1984). When compared with a control group of 1350 workers, the relative risk was 5.1 ($p < 0.05$), but the multiple exposures, small sample size and lack of quantitative exposure data precludes conclusions about a causal effect. Ethyl acetate was negative for reverse mutations in S. typhimurium in the presence of S-9 (Ishidate et al., 1984) and in a micronucleus assay in mice (Hayashi et al., 1981). It did, however, induce aneuploidy in a yeast cell line (Zimmerman et al., 1985) and polyploidy and chromosomal aberrations in a mammalian cell line (Ishidate et al., 1984) in the absence of metabolic activation. There are no data on the reproductive toxicity to mammals of ethyl acetate.

Rats treated by gavage with 3600 mg/kg/day ethyl acetate for 90 days had reduced food consumption and body weight gain, increased incidences of overt clinical signs of toxicity and organ weight changes, including reduced absolute and relative kidney and liver weights (American Biogenic Corp., 1986). No effects were observed at 900 or 300 mg/kg/day. Subchronic exposure of three guinea pigs to 2000 ppm ethyl acetate, 4 hours/day, 6-7 hours/week, led to no measurable changes in body weight gains, or in

hematological or urinary values (Smyth and Smyth, 1928). The U.S. EPA (1986a) recently verified an RfD of 0.9 mg/kg/day or 63 mg/day for a 70 kg man for ethyl acetate based on the subchronic oral rat study by American Biogenic Corp. (1986). The RfD was calculated by dividing the NOEL of 900 mg/kg/day in the 90-day gavage study in rats by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 to protect sensitive individuals and 10 to approximate chronic exposure). No additional data were located that would alter this value; therefore, the RfD of 0.9 mg/kg/day (63 mg/day) is recommended until further carcinogenic, reproductive, subchronic or chronic toxicity studies become available.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Chronic oral and inhalation studies of ethyl acetate could not be located in the available literature as cited in the Appendix, but a subchronic oral and a subchronic inhalation study were available. In the inhalation study, no effects were observed in guinea pigs exposed to 2000 ppm (7206 mg/m³), 4 hours/day, 6-7 hours/week for 65 exposures (Smyth and Smyth, 1928). In the oral study, however, decreased growth rates, organ weight changes and clinical signs of toxicity were observed in rats treated by gavage with 3600 mg/kg/day (American Biogenics Corp., 1986) (Table 9-1). Hematological, clinical chemistry and urinalysis test, and ophthalmological, gross and histological examination revealed no treatment-related effects at 300, 900 or 3600 mg/kg/day. The highest RV_e that can be assigned to the effects observed at 3600 mg/kg/day is 7 because of the CNS toxicity. Multiplying the dose by the cube root of the ratio of the average body weight of the female rats (0.23 kg) in the study to the reference human weight (70 kg) and by 70 kg, and dividing by an uncertainty factor of 10 to approximate chronic exposure results in an MED of 3746 mg/day (Table 9-2). The MED corresponds to an RV_d of 1 which, when multiplied by the RV_e , results in a CS of 7, corresponding to an RQ of 1000 (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The available carcinogenicity data of ethyl acetate were discussed in Section 5.1. No chronic bioassays in animals were available, but ethyl acetate was negative as a complete carcinogen when applied to the skin of mice (Lindenfelser et al., 1974) and in the pulmonary adenoma assay when injected intraperitoneally in mice (Stoner et al., 1973). The available animal evidence for the carcinogenicity of ethyl acetate is considered to be

TABLE 9-1
Oral Toxicity Summary for Ethyl Acetate in Sprague-Dawley Rats*

Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response
M	30	0.37	corn oil	99.9%	3600 mg/kg/day for 90 days	3600	Reduced body weight gain and food consumption; decreased absolute and relative kidney weights and absolute spleen weight and increased testes weight (males); increased incidences of salivation, irregular breathing and lethargy (males and females); decreased relative liver weights (males and females)
F	30	0.23					

*Source: American Biogenics Corp., 1986

TABLE 9-2
Oral Composite Scores for Ethyl Acetate in the Rat^a

Animal Dose (mg/kg/day)	Human MED (mg/day)	RV _d	Effect	RV _e	CS	RQ
3600 for 90 days	3746 ^b	1	signs of CNS toxicity	7	7	1000

^aSource: American Biogenics Corp., 1986

^bThe dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-3

Ethyl Acetate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	3746 mg/day
Effect:	CNS toxicity (increased salivation, irregular breathing, lethargy)
Reference:	American Biogenics Corp., 1986
RV_d:	1
RV_e:	7
Composite Score:	7
RQ:	1000

***Equivalent human dose**

inadequate. It is worth noting that ethyl acetate is metabolized to ethanol and that ethanol may present an additional cancer toxicity hazard. Additionally, ethanol is metabolized to acetaldehyde which is carcinogenic.

Of 15 cases of leukemia in a cohort of 6678 workers in the rubber industry, 11 cases were found in the group potentially exposed to 24 solvents other than benzene (Arp et al., 1983). Of these 11 cases, 3 had been exposed to ethyl acetate, among other solvents (Checkoway et al., 1984). When compared with a control group of 1350 workers, the relative risk was 5.1 ($p < 0.05$), but the multiple solvent exposure, small sample size and lack of quantitative exposure data precludes conclusions regarding a causal effect of ethyl acetate, or any of the other solvents. Thus, the available epidemiologic data is judged to be inadequate for assessing the carcinogenic potential of ethyl acetate.

Ethyl acetate was negative for reverse mutations in *S. typhimurium* in the presence of S-9 (Ishidate et al., 1984) for point mutations and recombination in *S. cerevisiae* (Zimmerman et al., 1985) and in the micronucleus assay in mice (Hayashi et al., 1981). Ethyl acetate induced aneuploidy in *S. cerevisiae* (Zimmerman et al., 1985) and chromosome aberrations in Chinese hamster lung fibroblasts (Ishidate et al., 1984).

Because the evidence in animals and humans is inadequate, ethyl acetate is classified as a U.S. EPA Group D chemical meaning that it is not classifiable as to its human carcinogenicity (U.S. EPA, 1986b). It is worth noting that ethyl acetate is metabolized to ethanol which may present an additional cancer hazard risk. Furthermore, ethanol is metabolized to acetaldehyde which is carcinogenic in animal test systems.

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Zimmermann, F.K., V.W. Mayer, I. Scheel and M.A. Resnick. 1985. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. *Mutat. Res.* 149: 339-351.

APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

Jaber, H.M., W.R. Mabey, S.T. Liu, T.W. Chow and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest in the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.